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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,223	TYAGI ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *117-132* is/are pending in the application.

4a) Of the above claim(s) *130-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *117-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 117-129, in the reply filed on September 18, 2007 is acknowledged. The traversal is on the ground(s) that the method of Group I (claims 117-129) and the kit of Group II (claims 130-132) share a special technical feature linking them over the prior art. This argument was not found persuasive, because as discussed previously and in greater detail below, the combined teachings of Chakravorty, Jaber, and Nair render the method of claims 117-126 prima facie obvious. Therefore, the claims do not possess a special technical feature linking them over the prior art, and a lack of unity requirement is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 130-132 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 18, 2007.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

2. The abstract of the disclosure is objected to because it uses legal phraseology, specifically the phrasing "said method" and "said primers". Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: The specification recites nucleic acid sequences that are greater than 10 nucleotides in length that have not been identified by the appropriate SEQ ID NO in accordance with 37 CFR 1.821 at page 33.

Appropriate correction is required.

Claim Interpretation

3. Claims 127-129 recite the use of PCR primers devRf2, devRr2, devRf3, and devRr3 that are designed from the devR gene of Mycobacterium tuberculosis. Claims 128 and 129 further recite the size of the amplification products generated using the devRf2/devRr2 and devRf3/devRr3 primer pairs. These claims do not recite SEQ ID NOS for the primers, and therefore, any primers designed from the devR gene of *Mycobacterium tuberculosis* are devRf2, devRr2, devRf3, and devRr3 primers.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 117-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 117-129 are indefinite because the scope of independent claim 117 is unclear. Claim 117 states that Solution 1 comprises a Universal Sample Processing solution composed of several components in lines 5-10. The use of the phrase "composed of" causes the scope of the claim to be unclear, because it is not clear whether the Universal Sample Processing solution consists of only the recited components or may further comprise additional elements. Replacement of "composed of" with "comprising" or "consisting of" as appropriate is suggested.

Claim 121 recites the limitation "the principal inhibitor removal component" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 122 recites the limitation "the principal decontaminating agents" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 123 recites the limitation "the principal mucolytic agent" in line 2. There is insufficient antecedent basis for this limitation in the claim.

The term "high bacillary load and/or lesser amount of junk-containing samples" in claim 124 is a relative term which renders the claim indefinite. This term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Furthermore, the term, "junk containing samples" is a subjective term, since different artisans will have different opinions as to whether a component in a given sample is "junk". As noted in MPEP 2173.05(b), "The phrase "aesthetically pleasing" was held indefinite because the meaning of a term cannot depend on the unrestrained, subjective opinion of the person practicing the invention. Datamize LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1347-48, 75 USPQ2d 1801, 1807 (Fed. Cir. 2005)."

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 117-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of Nair et al. (US 2001/0024801 A1; newly cited).

These claims are drawn to a method for processing clinical samples for analysis by smear, culture, or PCR methods using a composition comprising three solutions.

Regarding claim 117, Chakravorty teaches a method comprising:

(a) obtaining a clinical sample (page 114, section 2.1)

(b) mixing 1.5 – 2 volumes of a first solution to the sample and homogenizing the sample (see page 114, section 2.2.1, where solution 1 of Chakravorty comprises: 5 M GITC, 50 mM Tris-Cl, pH 7.5, 25 mM EDTA, 0.5% Sarcosyl, and 0.2 M β-mercaptoethanol)

(c) adding a second solution to the homogenate (solution 1 inherently includes water) and centrifuging to obtain a pellet (section 2.2.1 on page 114)

(d) washing the pellet with the first solution (page 114, section 2.2.2)

(e) washing the pellet of step (d) with water (page 114, section 2.2.2)

(f) resuspending the water-washed pellet in solution A (10% Chelex-100), solution B (Triton X-100 at 0.3%), and solution C (Tween 20 at 0.3%) (page 114, section 2.2.3).

Chakravorty further teaches that the resulting solution is used for PCR amplification of mycobacterial DNA (page 114).

Regarding claim 118, Chakravorty teaches homogenization for 30-60 seconds (page 114, column 1).

Regarding claim 119, Chakravorty teaches that the above process can be performed in approximately three hours (page 116, column 2).

Regarding claim 120, the 5 M concentration of GITC is about 4 M, about 5 M, and about 6 M, and the 0.2 M concentration of β-mercaptoethanol is about 0.1 M or about 0.2 M. This concentration of β-mercaptoethanol is also within the claimed range of 0.1-0.2 M. It is further noted that the intended use recitations "for processing samples for culture and smear", "for processing of samples for culture, smear, and PCR", and "samples processed for smear and PCR" have not been accorded patentable weight since they are intended use recitations (see MPEP 2111.02 II).

Regarding claims 121 and 122, Chakravorty teaches that the first solution described above is an inhibitor removal solution (pages 114-116). Since GITC is the major component of this solution, it is a principal inhibitor removal component and a principal decontaminating agent. Chakravorty also teaches that detergents serve a decontamination function (see page 115), and therefore, the sarcosyl present in the first solution of Chakravorty is a principal decontaminating agent.

Regarding claim 123, Chakravorty teaches that the first solution contains 0.2 M β-mercaptoethanol (page 114). This is inherently the principal mucolytic agent since it is the only mucolytic agent in the solution, as evidenced by Nair (see paragraph 28).

Regarding claim 124, Chakravorty teaches obtaining PCR-amplifiable DNA by adding 0.03% Triton X-100, which is within the claimed range of 0.01 - 0.1% (page 115, column 1). RNA is also inherently purified in the method of Chakravorty.

Regarding claim 125, the method of Chakravorty is performed at pH 7.5 (page 114).

Regarding claim 126, the samples used by Chakravorty were inherently stored at about -20°C for a time up to two months. It is also inherent that the samples can be processed for PCR, smear microscopy, and culture.

Chakravorty teaches the use of 5 M GITC in the first solution rather than 4-6 M GuHCl required by claim 117. Also, Chakravorty teaches that the above sample processing method can be performed in approximately three hours (page 116, column 2) rather than the 1-2 hours required by claim 119. Regarding claim 124, Chakravorty teaches lysis in the presence of 0.03% Triton X-100, but does not teach that this embodiment of the method is performed in the absence

of Solutions A, B, and C. Finally, regarding claim 125, Chakravorty teaches performing the method at a slightly alkaline pH of 7.5 rather than at neutral pH.

Jaber teaches a method for isolating DNA from *Mycobacterium tuberculosis* (pages 578-579). The method of Jaber comprises the following steps: (1) cell lysis in 6 M GuHCl, 50 mM EDTA, 1 mM 2-mercaptoethanol, 0.05% Tween 80; (2) ethanol precipitation, (3) washing with lysis buffer, (4) phenol-chloroform and chloroform-isoamyl alcohol extraction, and (5) ethanol precipitation (see page 579).

Regarding claim 117, Jaber teaches that the chaotropic agent guanidinium hydrochloride, (GuHCl), "inactivates DNase and RNase, dissociates nucleoprotein, and disturbs cellular and subcellular structure, and its pH and ionic strength favor the native form of DNA (page 579, column 2)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute GuHCl for GITC in the sample processing method taught by Chakravorty. An ordinary artisan would have been motivated to do so, because as evidenced by the teachings of Jaber (page 579-580), GuHCl and GITC are art-recognized equivalents useful for the same purpose. As noted in MPEP 2144.06, substitution of art-recognized equivalents useful for the same purpose is prima facie obvious. Furthermore, an ordinary artisan would have recognized that unlike GITC, GuHCl is nontoxic, and therefore, would have been motivated to use this non-toxic equivalent in order to minimize the use of hazardous chemicals in the method of Chakravorty. An ordinary artisan also would have been motivated to perform the method of Chakravorty using Triton X-100 in the absence of solutions A, B, and C, because Chakravorty taught that this detergent resulted in the best lysis and inhibitor removal (page 115) and that the

Chelex-100 adsorption step (i.e. solution A treatment) only served to remove residual inhibitors that would not be present in samples with a low level of contaminants (page 116). An ordinary artisan would have been motivated to eliminate unnecessary processing steps, such as treatment with solutions A, B, and C, because Chakravorty taught that multi-step processes resulted in sample loss and presented more contamination opportunities (page 116). Finally, regarding claims 118, 119, and 125, an ordinary artisan would have been motivated to optimize the homogenization time, the total processing time, and the pH at which the method was conducted in order to achieve the desired results. For example, an ordinary artisan would have been motivated to optimize the homogenization time in order to obtain maximal lysis without damaging the DNA. An ordinary artisan also would have been motivated to minimize the time required for performance of the method in order to increase efficiency. Moreover, as noted in MPEP 2144.05, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." Routine optimization is not inventive and no evidence has been presented to suggest that the selection of the claimed homogenization times, processing times, or pH values was other than routine or that the results should be considered to be unexpected compared to the prior art. Therefore, the methods of claims 117-126 are prima facie obvious in view of the combined teachings of Chakravorty, Jaber, and Nair in the absence of secondary considerations.

7. Claims 127-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of Nair (US 2001/0024801 A1; newly cited) and further in view of GenBank Accession No. U22037 (March 1999; newly cited) and further in view of Marchetti et al. (Journal of Clinical Microbiology (1998) 36(6): 1512-1517; newly cited) and further in view of Buck et al. BioTechniques (1999) 27(3): 528-536; newly cited).

The combined teachings of Chakravorty, Jaber, and Nair result in the method of claims 117-126, as discussed above.

Regarding claims 127-129, Chakravorty teaches using a set of primers designed from the *Mycobacterium tuberculosis* devR gene to amplify DNA isolated using the above method (page 114, column 2). However, Chakravorty does not teach amplification using two sets of primers, wherein each primer set targets the devR gene and produces amplification products of 308 bp and 164 bp.

GenBank Accession No. U22037 teaches the complete nucleotide sequence of the *Mycobacterium tuberculosis* devR gene. The primers taught by Chakravorty are contained in this sequence and produce a 513 bp amplification product.

Marchetti teaches methods for amplifying *Mycobacterium tuberculosis* DNA by PCR (see abstract and page 1513). Marchetti compared the sensitivity of four different PCR primer pairs and determined that the use of primers designed to amplify shorter targets resulted in more sensitive detection than primers designed to amplify longer targets (see abstract and pages 1514-1515). Marchetti further stated, "PCR3 and PCR4, whose final amplification products are 106

and 123 bp long, respectively, showed the best results in terms of sensitivity compared to those of PCR1 and PCR2, which amplify longer fragments (223 and 143 bp, respectively). This suggests the need to choose the correct primers, with those amplifying relatively shorter DNA sequences, which are thus less prone to fragmentation, being favored (page 1515, column 2)."

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize any set of primer pairs designed from the known *Mycobacterium tuberculosis*

devR gene to amplify DNA isolated by the method resulting from the combined teachings of Chakravorty, Jaber, and Nair. Since Marchetti taught that the use of primers designed to amplify short targets in the *Mycobacterium tuberculosis* genome resulted in increased sensitivity (pages 1514-1515), an ordinary artisan would have been motivated to design primer pairs targeting sequences shorter than the 513 bp region targeted by Chakravorty. An ordinary artisan would have had a reasonable expectation of success designing these primers since the complete devR gene sequence was known in the art at the time of invention as evidenced by GenBank Accession No. U22037. An ordinary artisan also would have had a reasonable expectation of success in using the primers in the method resulting from the combined teachings of Chakravorty, Jaber, and Nair since Buck demonstrated that essentially all primers were capable of an equivalent degree of extension when hybridized to a complementary target. Therefore, absent any secondary considerations, the claimed methods are prima facie obvious in view of the combined teachings of Chakravorty, Jaber, Nair, Marchetti, GenBank Accession No. U22037, and Buck.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding the dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty, Jaber, and Nair. The complete

nucleotide sequence of the Mycobacterium tuberculosis gene disclosed in GenBank Accession No. U22037 presented the ordinary artisan with a finite number of possible primers for amplification. Then, since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by applying the teachings of Marchetti to the devR gene targeted by Chakravorty. Therefore, the methods of claims 127-129 are *prima facie* obvious over the cited references in the absence of secondary considerations.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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November 24, 2007
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